Clinical trial results:
A Phase 3, Open-label, Multicenter, Randomized Study of Sequential Zevalin (ibritumomab tiuxetan) versus Observation in Patients at least 60 Years of Age with Newly Diagnosed Diffuse Large B-cell Lymphoma in PET-negative Complete Remission after R-CHOP or R-CHOP-like Therapy

Summary

EudraCT number	2011-004916-51
Trial protocol	GB IE IT ES BE PT NL AT DE FR
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	15 August 2020
First version publication date	15 August 2020

Trial information

Trial identification

Sponsor protocol code	SPI-ZEV-11-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01510184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spectrum Pharmaceuticals, Inc.
Sponsor organisation address	157 Technology Drive, Irvine, United States,
Public contact	Phil Stevens, Acrotech Biopharma LLC., pstevens@acrotechbiopharma.com
Scientific contact	Phil Stevens, Acrotech Biopharma LLC., pstevens@acrotechbiopharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy and safety of the Zevalin study regimen compared to the 'Observation' arm in elderly patients in PET-negative complete response as defined by the Revised Response Criteria for Malignant Lymphoma, after first line R-CHOP or R-CHOP-like regimen.

Protection of trial subjects:

This protocol was conducted in accordance with the applicable Good Clinical Practices (GCP) regulations and guidelines, and in compliance with the principles of the “Declaration of Helsinki” (as amended in Tokyo, Venice,Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research was conducted.
An independent data monitoring committee (IDMC) was established for the purpose of reviewing patient safety and efficacy data. The IDMC was responsible for recommending whether the study should continue or stop early due to futility or safety concerns.

Background therapy:

Standard of care R-CHOP chemotherapy administered to patients prior to enrolment in the protocol.

Evidence for comparator:

Approximately 50-60% of patients presenting with DLBCL can be cured with a doxorubicin-based combination chemotherapy. Since the 1970s, CHOP has been the standard first-line therapy for patients with stage II-IV DLBCL. The CHOP regimen (cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m2 up to a maximum of 2 mg on day 1, and prednisone 40 mg/m2/day on days 1 to 5 every three weeks) is usually given for 6 or 8 cycles. Numerous studies have been performed during the last decades in an attempt to find chemotherapy regimens that are superior to CHOP alone. No alternative chemotherapeutic regimen has consistently shown improved results.
The addition of rituximab, an anti-CD20 monoclonal antibody improved outcomes in DLBCL. Superior results have been shown in elderly patients with a standard CHOP regimen to which rituximab was added (R-CHOP) This multicenter, randomized, clinical trial showed for all patients (including non-responders) a median 2-year OS rate of 70% in the R-CHOP patients, compared with 57% in the CHOP arm. This study was the basis for the EU approval of rituximab (375 mg/m2) to be given in combination with standard CHOP in patients with DLBCL over 60 years of age. An update after a median follow-up of 5 years, demonstrated a relapse rate of 20% and a 5-year OS rate of 58% for the R-CHOP arm, which supports the concept that unrealized minimal residual disease exists in patients despite achieving a CR/CRu.
In this study patients in the observation arm must have received 6 cycles of R-CHOP or R-CHOP-like treatment to be eligible.

Actual start date of recruitment	01 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	United Kingdom: 9

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 6
Worldwide total number of subjects	79
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	77
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 79 patients were recruited across 10 countries.

Pre-assignment

Screening details:

Patient eligibility during the trial was assessed according to the eligibility criteria within the current version of the protocol at the time the patient was enrolled.

Pre-assignment period milestones

Number of subjects started	79
Number of subjects completed	79

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Zevalin treated

Arm description:

Patients receive rituximab on day 1 followed by rituximab on Days 7-9, and Y-90-Zevalin 4 hours later.

Arm type	Experimental
Investigational medicinal product name	Zevalin
Investigational medicinal product code	PRD17186
Other name	
Pharmaceutical forms	Kit for radiopharmaceutical preparation
Routes of administration	Intravenous use

Dosage and administration details:

One administration of Zevalin on Day 7-9.
Days 7-9: Rituximab 250 mg/m2 intravenous infusion, followed 4 hours later by Y-90-Zevalin 0.4 mCi/kg 10-minute intravenous push (0.3 mCi/kg in patients with a platelet count in 100,000/µL to 149,000/µL).

Investigational medicinal product name	Rituximab
Investigational medicinal product code	PRD00304MIG
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single treatment on Day 1 and Day 7-9.
Day 1: Rituximab 250 mg/m2 intravenous infusion.
Days 7-9: Rituximab 250 mg/m2 intravenous infusion, followed 4 hours later by Y-90-Zevalin.

Arm title	Observation

Arm description:

Patients receive standard of care treatment i.e. R-CHOP or R-CHOP like therapy.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Zevalin treated	Observation
Started	36	43
Completed	0	0
Not completed	36	43
Trial closure	28	28
Disease progression	1	2
Patient withdrawal	1	4
Lost to follow-up	-	8
Bone marrow positive for DLBCL after randomization	-	1
Lost to follow-up	6	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall study (overall period)

Reporting group description: -

Reporting group values	Overall study (overall period)	Total	
Number of subjects	79	79	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults (59-85 years)	79	79	
Age continuous Units: years			
median	70		
full range (min-max)	59 to 85	-	
Gender categorical Units: Subjects			
Female	42	42	
Male	37	37	
Race Units: Subjects			
White	73	73	
Asian	1	1	
Black	1	1	
Other	2	2	
Unknown	2	2	
Ethnicity Units: Subjects			
Not Hispanic or Latino	73	73	
Hispanic or Latino	4	4	
Not reported	2	2	
ECOG Units: Subjects			
0-Fully active	46	46	
1-Restricted	31	31	
2-Ambulatory	2	2	

End points

End points reporting groups

Reporting group title	Zevalin treated
Reporting group description:	
Patients receive rituximab on day 1 followed by rituximab on Days 7-9, and Y-90-Zevalin 4 hours later.	
Reporting group title	Observation
Reporting group description:	
Patients receive standard of care treatment i.e. R-CHOP or R-CHOP like therapy.	

Primary: Overall survival

End point title	Overall survival[1]

End point description:

The analysis description was further differentiated into 'living patients' and 'patients who died' in both the Zevalin and Observation arms.
The median Overall Survival for living patients treated with Zevalin (8.9 months) was numerically greater than for patients in the Observation group (6.1 months). This was also true for the one patient who died in the Zevalin group (16.8 months) and the two patients in the Observation group (5.8 months).

End point type	Primary

End point timeframe:

Overall survival as defined by the time between date of randomisation and death of patient due to any cause

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Study terminated early for business reasons and the primary efficacy analysis could not be completed due to incomplete enrolment. All analysis was descriptive.

End point values	Zevalin treated	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[2]	43[3]		
Units: months				
median (full range (min-max))				
Living patients	8.9 (2.7 to 22.6)	6.6 (0.07 to 21.3)		
Patients who died	16.8 (16.8 to 16.8)	5.8 (1.9 to 9.7)		

Notes:

[2] - living patients = 35 + patients who died = 1

[3] - living patients = 41 + patients who died = 2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent of the patient to Day 90 all adverse events were collected. From Day 91 only adverse events related to study treatment were collected.

Adverse event reporting additional description:

Safety population was used in all analyses of safety. Safety data of patients who received any study treatment was compared to safety data of patients who received no study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Zevalin

Reporting group description:

All randomized patients who received any element of Zevalin treatment including rituximab were classified in to the Zevalin treatment regimen arm.

Reporting group title	Observation

Reporting group description:

Patients randomised to the observation arm who did not receive any further anti-lymphoma therapy unless they had a relapse of their disease

Serious adverse events	Zevalin	Observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 36 (22.22%)	3 / 43 (6.98%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed Level of Consciousness			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 36 (11.11%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 36 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Zevalin	Observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 36 (58.33%)	14 / 43 (32.56%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Transitional cell carcinoma			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Embolism			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 36 (27.78%)	2 / 43 (4.65%)	
occurrences (all)	15	2	
Oedema			

subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Secretion discharge			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 36 (8.33%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Investigations			

Platelet count decreased			
subjects affected / exposed	6 / 36 (16.67%)	0 / 43 (0.00%)	
occurrences (all)	11	0	
Neutrophil count decreased			
subjects affected / exposed	6 / 36 (16.67%)	0 / 43 (0.00%)	
occurrences (all)	13	0	
White blood cell count decreased			
subjects affected / exposed	6 / 36 (16.67%)	0 / 43 (0.00%)	
occurrences (all)	11	0	
Lymphocyte count decreased			
subjects affected / exposed	4 / 36 (11.11%)	0 / 43 (0.00%)	
occurrences (all)	13	0	
Blood potassium decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 36 (8.33%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Dizziness			
subjects affected / exposed	2 / 36 (5.56%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Dysgeusia			

subjects affected / exposed	2 / 36 (5.56%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Disturbance in attention			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 36 (2.78%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 36 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	6 / 36 (16.67%)	0 / 43 (0.00%)	
occurrences (all)	15	0	
Neutropenia			
subjects affected / exposed	4 / 36 (11.11%)	1 / 43 (2.33%)	
occurrences (all)	9	1	
Anaemia			
subjects affected / exposed	5 / 36 (13.89%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Leukopenia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	5 / 36 (13.89%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	4 / 36 (11.11%)	1 / 43 (2.33%)	
occurrences (all)	6	1	
Diarrhoea			
subjects affected / exposed	3 / 36 (8.33%)	3 / 43 (6.98%)	
occurrences (all)	5	4	
Vomiting			
subjects affected / exposed	2 / 36 (5.56%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Haemorrhoids			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 36 (5.56%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Blister			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Dermal cyst			

subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Dermatitis bullous			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 36 (8.33%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	2 / 36 (5.56%)	2 / 43 (4.65%)	
occurrences (all)	3	3	
Arthralgia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Jaw disorder			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Musculoskeletal pain			

subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Skin bacterial infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Pseudohyperkalaemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			

subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2012	Summary of significant changes as follows: • Study population – utilisation of official name of response criteria in study; bone marrow cellularity of >15% is only required for those patients randomised to Zevalin. Clarification to Methodology including: • Definition of risk groups • patient population • length of follow-up for safety assessment, • steps in the study, • response criteria to be used in study, • eligibility criteria, • inclusion and exclusion criteria, • description of patient number assignments made which include rationale for inclusion of follicular lymphoma grade 3B • randomisation process prior to study treatment • timeframe for collection of concomitant mediations • timing for screening activities • timing of bone marrow biopsy to confirm complete remission • screening procedures relating to pathology reports and secondary pathology review • Age-adjusted International Prognostic Index • Post-randomisation study procedures for both arms • Evaluation and timing of disease status, including use of MRI and applicability of neck imaging • Follow-up activities • Timing of survival follow-up • Secondary pathology confirmation procedures • Extended screening window for physical exams • Handling of abnormal laboratory values as adverse events • Timing of haematology laboratory testing • Electrolytes measures in serum laboratory testing • Timing of serum chemistry laboratory testing • Changes to study procedures • Method of assessing disease status • Occurrence of secondary malignancies regardless of timing and study arm reported as SAE • Collection of AEs • Timing and reporting of SAEs to Sponsor • Stratification

30 September 2012	Summary of significant changes as follows: • WHO classification 2008, as opposed to Revised European American Lymphoma used for confirmatory pathology review • Results updated for zevalin-randomised patients with the most current safety data • Zevalin Regimen scheduled to begin within 12 weeks of first day of last cycle of R-chemotherapy in line with Cheson 2007 response criteria Changes to inclusion criteria: - Confirmatory review was based on secondary reviews - H&E routine stain used for diagnostic purposes - Diagnostic CT scans performed 8 weeks after the first dose of the last cycle of R-chemotherapy. - PET-CT scans carried out in line with Cheson 2007 response criteria - Changes to blood counts monitored in line with standard practice • Changes to exclusion criteria including addition of pregnant and breastfeeding women and clarification of selection criteria • Changes to randomisation criteria in line with Cheson 2007 response criteria • Preparation and release of IMP to be carried out in line with local guidelines and current standard practice • Concomitant therapy updated with the current safety information • Clarification of study and screening procedures in line with Cheson 2007 response criteria • Clarification of study procedures in line with Zevalin regimen patients and evaluation of remission status • Clarification of secondary pathology confirmation • Clarification of screening activities • Change in duration of follow-up of study activities until relapse • Clarification of safety risks in relation to reproductive risks

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study terminated early for business reasons and the primary efficacy analysis could not be completed due to incomplete enrolment.

Notes: